CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

# SUMMARY OF TOXICOLOGY DATA
# ANCYMIDOL

Chemical Code # 001744, Tolerance # 50041
SB 950 # 248
Original date: February 1, 2002

## I. DATA GAP STATUS

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| Chronic toxicity, rat: | Data gap, no study on file. |
| Chronic toxicity, dog: | Data gap, no study on file. |
| Oncogenicity, rat: | Data gap, no study on file. |
| Oncogenicity, mouse: | Data gap, no study on file. |
| Reproduction, rat: | Data gap, no study on file. |
| Teratology, rat: | Data gap, inadequate study on file, no adverse effect indicated[a] |
| Teratology, rabbit: | Data gap, no study on file. |
| Gene mutation: | No data gap, no adverse effect. |
| Chromosome effects: | Data gap, inadequate study on file, no adverse effect indicated |
| DNA damage: | Data gap, inadequate study on file, no adverse effect indicated. |
| Neurotoxicity: | Not required at this time. |

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Toxicology one-liners are attached.
All record numbers through 114728 in 50041 - 009 were examined.
** indicates an acceptable study.
**Bold face** indicates a possible adverse effect.
File name: T020201
Prepared by J. Kishiyama and J. Gee, 2/1/02

[a] The RED of US EPA, 6/95, lists a rat teratology not on file with DPR. It also lists a 21-day dermal study in rabbits not on file. See the NOTES below. These studies should be submitted for evaluation by

the Department of Pesticide Regulation.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

No study submitted

### CHRONIC TOXICITY, RAT

No study submitted

### CHRONIC TOXICITY, DOG

No study submitted

### ONCOGENICITY, RAT

No study submitted

### ONCOGENICITY, MOUSE

No study submitted

### REPRODUCTION, RAT

No study submitted

### TERATOLOGY, RAT

50041 - 003 007189 Markham, J. K., E. R. Adams, N. V. Owen, W. R. Gibson and E. C. Pierce "A Teratology Study with Ancymidol Administered in the Diet to the Rat". (Eli Lilly and Co., Study R-142, August, 1972.) Ancymidol (purity not given, lot 866-250-OD-286) was fed in the diet at 0, 0.2, 0.4, or 0.8% of the diet (2000, 4000 and 8000 ppm) during gestation days 6 through 15 to 23, 23, 23, and 16 female Harlan rats, respectively. Initially, there were 25/group but due to faulty feeders, some did not receive the diet during days 11 to 17 and were eliminated from the study. Body weight and food consumption were depressed during the first week of treatment at 0.8% of the diet, returning to normal for the remainder of the study. There were no treatment-related effects on the fetuses. Maternal NOEL = 4000 ppm (body weight, food consumption). No adverse effects noted in the report. UNACCEPTABLE (no analyses of the diet, no purity of the test article, no individual data for body weight/food consumption data). Possibly upgradeable. (J. Wong, 6/28/85 and Gee, 1/29/02).

**NOTE**: The US EPA Reregistration Eligibility Standard for Ancymidol, June 1995, lists the following study which is not on file with the Department: Wright, F. and R. Clair "A developmental toxicity study of ancymidol (compound 069231) administered orally to CD rats." (Lilly, No. R33191, 1992). This study should be submitted for evaluation.

## TERATOLOGY, RABBIT

No study submitted

## GENE MUTATION

50041 - 009 114725 Bewsey, B. J. "The Effect of Ancymidol (EL-531, Compound 69231) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells". (Lilly Research Laboratories, Studies 850423MLA805 and 850501MLA805, June 1985.) Ancymidol (EL-531, Compound 69231, purity 99.8%, lot 247NB4) was tested at concentrations of 10 to 1000 µg/ml and 0.1 to 800 µg/ml without and with metabolic activation, respectively, for potential mutagenic effect on L5178Y mouse lymphoma cells. Cells were exposed for 4 hours, with a 48-hour expression time. There was a single culture per concentration with triplicate plates for mutation frequency in a single trial. Cell survival was determined as was appropriate. Concentrations were selected based on a preliminary test (850423MLA805), measuring suspension growth. Positive controls were functional. Total percent survival (suspension growth x cloning efficiency) was 83% or greater for 400 µg/ml and lower concentrations and 75% or lower for 600 µg/ml and higher. Only summary data were presented. Ancymidol (with and without S-9 Mix), under study conditions, did not increase mutation frequency. No adverse effect. UNACCEPTABLE (single trial). Not upgradeable. (Kishiyama and Gee, 1/29/02).

007 054682 Same study as 114725.

** 50041 - 009 114727 Rexroat, M. A. "The Effect of Ancymidol (EL-531, Compound 69231) on the Induction of Reverse Mutations in *Salmonella Typhimurium* Using the Ames Test." (Lilly Research Laboratories, Study 850325AMS805, May 1985) Ancymidol (EL-531, Compound 69231, purity 99.8%) was tested at concentrations of 0 (DMSO), 250, 500, 1000, 2500 and 5000 µg/plate with and without rat liver metabolic activation for mutagenic potential with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. There were triplicate plates per concentration, one trial. A preliminary toxicity assay with TA100 to concentrations of 5000 µg/plate indicated that ancymidol was not cytotoxic. Ancymidol at 5000 µg/plate showed no evidence of precipitation, cytotoxicity or increased revertants with any strain. The positive controls were functional. ACCEPTABLE with no adverse effect. (Kishiyama and Gee, 1/30/02).

007 054684 Same study as 114727.

50041 - 009 114728 Rexroat, M. A. "The Effect of Ancymidol (EL-531, Compound 69231) on the Induction of Bacterial Mutation using a Modification of the Ames Test." ( Lilly Research Laboratories, Toxicology Division, Study 850415GPA805, May, 1985.) Ancymidol (EL-531, Compound 69231, purity 99.8%) was tested at gradient concentrations ranging from 1000 to 100, 100 to 10, 10 to 1, and 1 to 0.1 µg/ml, with and without rat liver metabolic activation, for mutagenic potential with *Salmonella typhimurium* strains G46, C3076, D3052, TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* strains WP2 and WP2uvrA-. In this modification, agar slants were formed in 9 x 9 cm dishes and overlaid with a reverse wedge of agar containing the test article at 1000 ug/ml, etc. The gradient formed by diffusion of the chemical through the agar. Bacterial strains were streaked on the top of the agar and incubated for colony development. For activation, a thin layer containing the S9 and co-factors was added on top. Following incubation for 48 hours, the dishes were scored. No growth inhibition or increase in revertants was reported with any tester strain with Ancymidol, with and without

rat liver metabolic activation. Positive controls appeared to be functional. No adverse effect. UNACCEPTABLE.

Not upgradeable (non-replicated plates, maximum concentration used was not justified, considered a screening assay and dependent on diffusion). (Kishiyama and Gee, 1/30/02).

007 054685 Same study as 114728.

## CHROMOSOME EFFECTS

50041 - 009 114726 Neal, S. B. "The Effect of Ancymidol (EL-531, Compound 69231) on the *In Vivo* Induction of Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters." (Lilly Research Laboratories, Study 850715SCE805, October 1985.) Ancymidol (purity 99.8%, lot 247NB4) was administered orally (gavage) at doses of 200, 300, 400, or 500 mg/kg to three female Chinese hamsters/group. There were 2 females in the negative control group and one in the positive control. A BrdUrd tablet was implanted under the skin 5 hours before the single dose was given. After 19 hours of exposure, bone marrow cells were harvested and 25 metaphases per animal scored for sister chromatid exchanges. One hundred cells were scored to determine the percent in M1, M2 and M3. The positive control (cyclophosphamide) induced SCEs in metaphase and showed cytotoxicity by mitotic delay. There was no evidence of toxicity from ancymidol at 500 mg/kg with no mitotic delay. No evidence of the induction of SCE's was reported under the conditions of the study. No adverse effect. UNACCEPTABLE (no males tested without justification, too few animals per treatment group, no MTD indicated, no justification for the number of metaphases scored [25/animal]) Not upgradeable. (Kishiyama and Gee, 1/29/02)

007 054683 Same study as 114726.

## DNA DAMAGE

50041 - 007 054686 Hill, L. E. "The Effect of Ancymidol (EL-531, Compound 69231) on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes." (Lilly Research Laboratories, Studies 850402UDS805 and 850409UDS805, August 1985.) Ancymidol (EL-531, Compound 69231, purity 99.8%) was tested at concentrations from 0.5 to 1000 µg/ml for the induction of unscheduled DNA synthesis, using primary rat hepatocytes. In both studies, ancymidol at 500 µg/ml showed some cytotoxicity and lower concentrations (100 to 0.5 µg/ml) did not induce UDS. Ancymidol was too cytotoxic at 1000 µg/ml for evaluation (criteria were not given). There was one culture in each trial at each concentration. Twenty (20) cells were scored in each trial at each concentration. Only the initial cell viability was reported but the method used to determine it was not included. The only data presented were the mean (± SD) net nuclear grains per concentration per trial. No adverse effect noted from the data as reported. UNACCEPTABLE. Possibly upgradeable (viability information, detailed data for nuclear grain counts and cytoplasmic counts used to calculate the mean net nuclear grains/concentration). (Kishiyama and Gee, 1/30/02).

## NEUROTOXICITY

Not required at this time.

## OTHER

**NOTE**: The US EPA "Reregistration Eligibility Standard" for Ancymidol, June 1995, lists the following study, which is not on file with the Department. Wright, F., R. Glenn, D. Sites et al. "A 21-day subchronic dermal toxicity study of ancymidol (…) administered topically to New Zealand White rabbits." (Lilly, No. B11590, 1991). This study should be submitted to the Department for Review.

50041 - 003 007184 Chao, J. V./ N. V. Owen "Subacute toxicity." (Eli Lilly, Study R-600, 8/72) Ancymidol (purity not stated) was fed in the diet at 0, 0.2, 0.4 or 0.8% (2000, 4000 or 8000 ppm) to weanling Harlan rats for 3 months, 10/sex/group. The females at 0.8% grew less rapidly (mean body weight was 252 versus 291 for control females at termination, -13%). Hematology and limited clinical chemistry did not show any consistent effects. Relative organ weights showed some trend toward increase in the liver and kidney. There were no treatment-related effects at necropsy or in histopathology. Apparent NOEL = 4000 ppm. UNACCEPTABLE (no purity of the test article or analysis of the diets, no interim body weights, no ophthalmology, limited parameters for hematology and clinical chemistry and limited histopathology). Not upgradeable. No worksheet. (Gee, 1/29/02)

50041 - 003 007186 Owen, N. V. "Subacute toxicity." (Eli Lilly, Study D-376-70, 8/72) Beagle dogs, 2/sex/group, were given ancymidol (no purity given) in gelatin capsules at 0, 50, 100 or 200 mg/kg/day for 91 days. After 19 days, the high dose was administered half in the morning and half late in the afternoon. This change was the result of overt signs of CNS origin including nausea/vomiting, tremors, myoclonic jerking, and widespread stance. Most of the signs disappeared after splitting the dose. Doses were adjusted when there was a 10% change in the weekly body weight. Hematology, urinalysis and clinical chemistry parameters were measured at intervals. Organ weights were also measured. There were no gross changes at the terminal eye exam. There were no indications of treatment effects on hematology, urinalysis, bone marrow, organ weights, clinical chemistry (except possibly elevated alkaline phosphatase at 200 mg/kg), or histopathology. Nominal NOEL = 100 mg/kg/day (clinical signs). No adverse effect. UNACCEPTABLE (no purity of the test material, too few dogs per group, no food or water consumption data, limited pathology report (all negative), others). Not upgradeable. No worksheet. (Gee, 1/29/02)

50041 - 003 007188 Hoffman, D. G. "Effect of dietary administration of ancymidol on body weight, liver weight and *p*-nitroanisole metabolism in male rats." (Lilly, 1972) Ancymidol (no purity given) was fed in the diet to male rats at 0, 2000, 6000 or 18,000 ppm for 14 days with 10 in the control group and 4 in each treatment group. At termination, body weight, relative liver weight and *p*-nitroanisole O-demethylation were determined. Body weights were comparable, relative liver weight increased slightly but significantly at 6000 and 18000 ppm and the rate of *p*-nitroanisole O-demethylation increased at each dietary level, being significant at 6000 and 18000
ppm by Dunnett's t test. Data were presented in a single table as means standard errors. Report consisted of two pages. Supplemental data. No worksheet. (Gee, 1/29/02).

50041 - 003 007197 Arthur, B. H. "Rabbits - subacute dermal toxicity - study B-7032)." (Eli Lilly,

1972) New Zealand albino rabbits, 4/sex/group, were treated with A-REST solution (lot X-14920) at 0 (water control), 1:10, 1:4 or 1:2 aqueous dilution (equivalent to 0, 0.0135, 0.034 or 0.068 mg/kg active ingredient), 0.5 ml/kg, for 6 hours per day, 5 days per week for 4 weeks,

followed by 2 weeks of observation. The test material was put on a 2-ply gauze pad under occlusion. The 1:2 dilution was stated to be 10 times the recommended field concentration. The skin of 2/sex/group was abraded before the applications, being reabraded twice weekly, if necessary. The skin was examined daily and doses adjusted weekly for body weight. Blood and urine samples were taken pretest, at the termination of treatment and after the 2-week recovery period. After the recovery period, animals were terminated and organs and tissues taken for weights and histopathology. Urine and blood parameters were unaffected by treatment. Two deaths were unrelated to treatment. Occasional and transient erythema was reported in several exposed rabbits - no data. NOEL not determined from the data presented. No adverse effect. Supplemental data. No worksheet. (Gee, 1/29/02).

50041 - 003 007198 Owen, N. V. "Rats - subacute inhalational toxicity - study R-562." (Eli Lilly, 1972) Harlan rats, 10/sex/group, were exposed to A-REST (lot X-25017) at 0 (water) or 1:10 or 1:4 aqueous dilutions for 1 hour, 5 days per week, for 3 weeks, head only. These dilutions were equivalent to 1.66 and 4.08 micrograms of ancymidol per liter of air. Organs were weighed and selected tissues preserved and examined. There were no treatment-related effects on body weight, food consumption, hematology, limited clinical chemistry parameters (BUN, SGPT, glucose), relative organ weight, or pathology. Supplemental data (limited parameters only were recorded). NOEL was not determined from the data but apparently > 4.08 ug/liter/hour. No worksheet. (Gee, 1/29/02).